Applicants thank the Examiner for noting that the instant application was filed with informal drawings which are acceptable for examination purposes. Accordingly, Applicants will file formal drawings upon allowance of the instant application.

The title of the application has been amended to more clearly reflect the subject matter of the pending claims. Applicants respectfully request reconsideration of the pending claims.

I. REJECTIONS UNDER 35 U.S.C.§112

Claims 16, 18 and 19 stand rejected under 35 U.S.C. §112, second paragraph. Applicants respectfully traverse this rejection and believe that the rejection is moot in view of the amendments specifically removing the term "derived" or "derivative" from the rejected claims.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

Claims 13-20 stand rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse this rejection.

The Examiner acknowledges that the specification is enabling for an "immunoglobulin molecule which binds and neutralizes a preselected ligand and an immunologically active fragment thereof". Applicants believe that the amendment to claim 1, from which the other rejected claims depend, renders the rejection moot. Accordingly, Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §§102 and 103

Claims 13 and 15-20 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Stolle et al. (US Patent 4,748,018). Applicants respectfully traverse this rejection.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990). In re Bond, 15 USPQ 2d 1566 (Fed. Cir., 1990).

The office action states that Stolle et al. teaches a method of "passively immunizing a mammal against a preselected antigen from a pathogen by administering to said mammal a heterologous antibody from a fowl which has been specifically immunized against said antigen." (see page 4, paragraph 8). Stolle requires that the antigen is adminstered to a subject in order to induce an endogenous immune response in the subject. Applicants' method provides passive immunization with biologically active immunoglobulin molecules " which binds to and neutralizes said preselected ligand or immunologically active fragment thereof, wherein the immunoglobulin molecule is isolated from *plant cells* containing nucleotide sequences encoding one or more biologically functional immunoglobulin product not normally produced by the plant; and biologically functional immunoglobulin product encoded by said nucleotide sequences, wherein each nucleotide sequence encoding an immunoglobulin polypeptide encodes a leader sequence forming a secretion signal that is cleaved from said immunoglobulin polypeptide following proteolytic processing and wherein said immunoglobulin molecule is free from detectable sialic acid residues." [Emphasis added]

Clearly, the immunoglobulin molecules utilized in the Applicants' claimed method are not induced by an endogenous immune response to an antigen since they are produced in plants. Applicants specification teaches recombinant production of immunoglobulin molecules in plants, which teaching is absent in Stolle. Thus, Stolle does not teach each and every element of the claimed invention and cannot anticipate claims 13-20 or newly added claims 21-30. Accordingly, Applicants request that the rejection under 35 U.S.C. §102(b) be withdrawn.

Claims 13-20 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over Goodman et al. (US Patent No. 4,956,282) and During dissertation, in view of Stolle et al.

Applicants respectfully traverse this ground for rejection and submit that the currently claimed invention is not rendered obvious by Goodman et al or During, either when taken alone or in combination.

The Action alleges that the Goodman reference describes expression of biologically active immunoglobulins in transgenic plant cells for therapeutic purposes which can be administered to a subject without extraction from the plant cells in edible and nutritional plant parts. The Office Action also states that During teaches the method of expressing biologically active antibodies in transgenic plant cells. Stolle is added as teaching that immunization of a subject against a target pathogen would have provided a reasonable expectation of success.

Applicants respectfully disagree with the statements in the Office Action. First, the Goodman reference contains one statement regarding immunoglobulins (See column 3, lines 11-30). However, within the entire specification of Goodman, there is no other discussion of immunoglobulins. Rather, Goodman expresses a single chain polypeptide in a plant cell, but does not describe the expression and assembly of any immunoglobulin products. In other words, the Goodman reference speculates by the single above-quoted sentence that immunoglobulin heavy and light chains could be expressed and assembled in a plant cell. At best Goodman provides an invitation to experiment and does not teach cleavable leader sequences which Applicants have shown are essential to producing biologically active immunoglobulin molecules for use in the claimed invention.

In other words, contrary to the assertions of the Action, Goodman does not provide sufficient motivation or suggestion for one skilled in the art to use the methods for the production of immunoglobulins because Goodman does not describe procedures for production of any immunoglobulin product at all. Goodman is unaware of requirements for production of immunoglobulin products in plants is because the disclosures of Goodman are silent on this

point. Thus, it cannot be said that Goodman provides any guidance whatsoever to solve the particular problem of expression and assembly of immunoglobulin products in plants for any use.

It is pertinent to note that the specification of the Goodman patent has been interpreted relatively narrowly with respect to enablement. In the case *In re Goodman*, 29 U.S.P.Q.2nd 2010, 2013 (Fed. Cir. 1993), the Federal Circuit opined upon the disclosure of a continuation of the herein cited patent and noted that "Goodman's specification contains a single example of producing gamma-interferon in the dicotyledonous species, tobacco. This single example, however, does not enable a biotechnician of ordinary skill to produce any type of mammalian protein in any type of plant cell." Accordingly, the breadth of enablement accorded Goodman by the Examiner is inconsistent with its judicial interpretation and thus this reference should not be viewed as teaching anything in particular with respect to production of immunglobulins in plants.

In addition, Goodman remains deficient in that it does not teach each nucleotide sequence encoding an immunoglobulin polypeptide encoding a leader sequence forming a secretion signal that is cleaved from the immunoglobulin polypeptide following proteolytic processing.

The combination of Goodman with During cannot remedy the deficiencies of Goodman. During suffers from many deficiencies in and of itself, including: cleavage site ambiguity in the leader sequence is a consequence of the During strategy. The leader sequence strategy used by During did not result in experimental success and the During results as a whole are discouraging as During himself indicates by noting: (i) very low levels of accumulation, (ii) no detection of heavy chain, (iii) immunoglobulin accumulated in the cytoplasm, (iii) absence of direct evidence for assembly, (iv) inefficient assembly by indirect measurement, and (v) predominant accumulation in chloroplasts. Moreover, plant cell secretion is not observed as no association of antibody with the cell wall is observed. Accordingly, those of skill in the art would not have recognized the During strategy as providing reasonable commercial applicability and in fact,

During teaches away from the presently claimed methodology for use of plant-assembled antibodies in plants as the results of During are questionable at best. Furthermore, During clearly does not teach or suggest any functional leader sequence that is cleaved following proteolytic processing and neither During nor the art at the time suggest how one would create such a functional leader/secretion sequence in a plant cell.

Further, the During strategy could not be obvious due to the contrasting nature of the results obtained by During and those obtained by the present inventors. During struggled to obtain immunologically detectable levels of expression, noting:

"A method therefore had to be developed that permits the sought protein to be enriched from the crude extract before Western blot or preferably to be isolated and concentrated to detectable concentrations".(page 87, last full paragraph)

"By direct Western blotting from the crude extract of calli or induced plant material, only unsatisfactory results can be achieved".(page 89, first sentence of first full paragraph)

"The difficult reproducibility of biological material is particularly clear in these analyses, precisely when inductions are carried out. The total found amounts of antibody protein lies in the lowermost range of the detection limits and therefore form only a very limited fraction of the total protein of the transformed plants." (page 89, last full paragraph) (All Page numbers used in the discussion immediately above are based upon the fully translated version of the During Dissertation submitted herewith).

Contrary to the ineffective strategy set forth by During the present inventors achieve clearly detectable and useful levels of immunglobulins in crude extracts. For example, representative expression of 200 to 500 micrograms of SIgA-G per gram of plant material (See, *e.g.*, instant specification page 99, lines 22-23) and 2 to 1400 ng/mg of plant protein for IgG

chains (See, *e.g.*, instant specification page 68, lines 15-26) is evidenced by the instant specification.

The unexpected and surprising results of using plants to process, assemble, and secrete immunoglobulin products by the methods set forth in the present application is not only supported by the instant specification and the prior art, but also by the fact that the results were so surprising that the present inventor's work was featured on the cover of the prestigious journal Nature (Nov 2;342(6245):76-78, 1989).

Accordingly, given the above remarks, it is clear that not only does During lack an enabling disclosure and teach away from the present invention, but the results obtained by the present inventors were clearly unexpected and surprising to the scientific community, especially in light of the lack of success demonstrated by During.

Stolle has been discussed above and Applicants submit that the addition of Stolle to Goodman and During cannot remedy the later references' failures to teach or suggest the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 13, and 15-30 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: 5/21/01

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Version with changes showing markings:

13. (amended) A method of passively immunizing a human or animal subject against a preselected ligand, comprising administering to said subject a prophylactic amount of a biologically active immunoglobulin molecule [capable of binding] which binds to and neutralizes said preselected ligand or immunologically active fragment thereof, wherein the immunoglobulin molecule is isolated from plant cells containing nucleotide sequences encoding one or more biologically functional immunoglobulin product not normally produced by the plant; and biologically functional immunoglobulin product encoded by said nucleotide sequences, wherein each nucleotide sequence encoding an immunoglobulin polypeptide encodes a leader sequence forming a secretion signal that is cleaved from said immunoglobulin polypeptide following proteolytic processing
[a preselected ligand,] and wherein said immunoglobulin molecule is free from detectable sialic acid residues.

14. (Canceled) The method of claim 13, wherein said immunoglobulin molecule is encapsulated in a plant cell.

16. (Amended) The method of claim 15, wherein said material having nutritional value is [derived] from a plant or an animal.

18. (Amended) The method of claim 13, wherein said immunoglobulin is an antibody or an immunologically active [derivative or] fragment thereof.

19. (Amended) The method of claim 13, wherein said immunoglobulin is secretory IgA or an immunologically active [derivative or] fragment thereof.

Please add the following new claims:

--21. The method of claim 20, wherein the pathogen is selected from bacteria, viruses, or parasites.

22. The method of claim 20, wherein the pathogen is E. coli, Salmonellae, Vibrio cholerae, Salmonellae typhimurium, or Streptococcus mutans.

23. The method of claim 13, wherein the plant is a monocot.

24. The method of claim 13, wherein the plant is a dicot.

25. The method of claim 13, wherein the leader sequence is a non-native leader sequence.

26. The method of claim 25, wherein the leader sequence is a yeast leader sequence.

27. The method of claim 25, wherein the leader sequence is a plant leader sequence.

28. The method of claim 13, wherein the plant cells are from seeds. (support in the examples and definitions)

29. The method of claim 13, wherein the immunoglobulin molecule is an IgA molecule.

30. The method of claim 13, wherein the immunoglobulin molecule is an IgG molecule.--